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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,387	10/25/2005	Yoseph Shaaltiel	30570	1887

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
10/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,387	SHAALTIEL ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *154-167* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *154-167* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :5/4/2010, 5/20/2010, 7/15/2010, 7/19/2010, 7/27/2010, 9/6/2010, 8/9/2010, 8/23/2020, 8/30/2010, 8/3/2010, 9/19/2010, and 11/15/2009 .

DETAILED ACTION

Status of the Application

Claims 154-167 are pending.

Applicant's amendment cancelling claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146, and adding claims 154-167 as submitted in a communication filed on 8/17/2010 is acknowledged.

New claims 154-167 are directed to the invention previously examined. These claims are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statements (IDS) submitted on 5/4/2010, 5/20/2010, 7/15/2010, 7/19/2010, 7/27/2010, 9/6/2010, 8/9/2010, 8/23/2020, 8/30/2010, 8/3/2010, 9/19/2010, and 11/15/2009 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Rejections - 35 USC § 112, Second Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 158 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. this is a new rejection necessitated by amendment.

4. Claim 158 is indefinite in the recitation of "the….protein of claim 154, an increased affinity for, and uptake into macrophages, in comparison with….., and having…activity" because one cannot

determine how claim 158 is further limiting claim 154. The term is completely unclear. For examination purposes, no patentable weight will be given to the limitations recited in claim 158. Claim 158 will be interpreted as a duplicate of claim 154.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 154-167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garger et al. (U.S. Publication 2002/0088024, published 7/4/2001; application No. 09/993059 filed on 11/13/2001), as evidenced by GenBank accession number P04062 GLCM_HUMAN GI:121283 (April 1, 1993) in view of Boller et al. (U.S. Patent No. 6054637, issued 4/25/2000) and further in view of Frijters et al. (NL-1012782, published 2/6/2001). This rejection was previously applied to now canceled claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146. It is applied to new claims 154-167 for the reasons of record and those set forth below.

Garger et al. teach the recombinant production of human glucocerebrosidase in transgenic tobacco plants (Examples 1-7; called rGCB). Garger et al. teach (page 4, paragraph [0032]) that their human glucocerebrosidase is that disclosed by Tsuji et al. (J. Biol. Chem. 261:50-53, 1986) and Sorge et al. (PNAS 82:7289-7293, 1985). Thus, the human glucocerebrosidase of Garger et al. comprises SEQ ID NO: 8 as evidenced by GenBank accession number P04062, locus GLCM_HUMAN, GI:121283, since this GenBank entry cites Tsuji et al. and Sorge et al. as references associated with the protein disclosed in that entry. See alignment provided in a prior Office action. Garger et al. also teach the enzymatic removal of sialic acid, galactose, and N-acetylglucosamine residues to prepare glucocerebrosidase for therapy (page 14, paragraph [0164], lines 12-15; page 1, paragraph [0006], lines 18-26) and that their rGCB co migrates with the mannose-terminal therapeutic glycoform. Garger et al. teach that one of the uses for the recombinant rGCB produced in plants is for therapy (page 6, paragraph [0045]). As known in the art, xylose residues and core alpha (1-3) fucose residues are added to proteins in plants during the glycosylation process. Garger et al. teach that the rGCB produced in transgenic tobacco plants has xylose and fucose residues (page 13, paragraph [0125], last two sentences). Also, as known in the art, removal of sialic acid, galactose, and N-acetylglucosamine residues would result in mannose residues being exposed. The instant reference further teaches the purification of the rGCB (Example 5). Garger et al. do not teach the human glucocerebrosidase linked at the N-terminus to the endoplasmic reticulum signal peptide of SEQ ID NO: 1 and linked at the C-terminus to the basic tobacco chitinase A gene vacuolar targeting signal peptide of SEQ ID NO: 2.

Boller et al. teach that one of the advantages in directing proteins to the vacuole is due to the fact that vacuoles constitute the largest storage compartment in plants for dissolved substances (column 2, line 57-column 3, line 1). Boller et al. teach several signal peptides for vacuolar sorting including a tobacco chitinase gene vacuolar targeting signal peptide which comprises SEQ ID NO: 2 (SEQ ID NO: 29 in that patent). See alignment provided with a prior Office action. Boller et al. disclose adding the DNA

encoding the vacuolar targeting signal peptide at the 3' end of any desirable expressible DNA (C-terminus of the corresponding protein). As such, Boller et al. teach adding the vacuolar signal peptide to the C-terminus of any desired protein (column 8, lines 38-52). Boller et al. do not teach the polypeptide of SEQ ID NO: 8.

Frijters et al. teach an N-terminal endoplasmic reticulum signal sequence which is identical to that of SEQ ID NO: 1 (page 17, lines 10-18; MKTNLFLFLIFSLLLSLSSAEF; SEQ ID NO: 3, page 30) which was linked to an *A. victoria* GFP variant to direct this variant to the ER. See alignment provided with a prior Office action. Frijters et al. do not teach the protein of SEQ ID NO: 8.

Claims 154-167 are directed in part to (1) a protein which comprises SEQ ID NO: 14 wherein said protein is glycosylated and comprises at least one exposed mannose, at least one fucose having an alpha(1-3) glycosidic bond, and at least one xylose, (2) a plant cell which expresses the protein of (1), (3) a pharmaceutical composition comprising the protein of (1) and (4) a pharmaceutical composition comprising the plant cell of (2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make in plant cells a fusion protein comprising the endoplasmic reticulum signal peptide of Frijters et al. (SEQ ID NO: 1) linked to the N-terminus of the human glucocerebrosidase of Garger et al. (SEQ ID NO: 8), and the vacuolar signal peptide of Boller et al. (SEQ ID NO: 2) linked at the C-terminus of the human glucocerebrosidase of Garger et al. to obtain the polypeptide of SEQ ID NO: 14. A person of ordinary skill in the art is motivated to construct such fusion protein because (1) Boller et al. teach the advantages of directing a desired protein to the vacuole of a plant, and (2) the human glucocerebrosidase of Garger et al. requires glycosylation. As known in the art and taught by Garger et al., the initial steps in the glycosylation process take place in the endoplasmic reticulum (page 3, paragraph [0025]). Therefore, adding an ER signal to the human glucocerebrosidase of Garger et al. would direct this protein to the ER for glycosylation. One of ordinary skill in the art has a reasonable expectation of success at making the

fusion protein of Garger et al., Boller et al. and Frijters et al. since Boller et al. and Frijters et al. teach fusion proteins comprising said signal peptides, and the use of fusion proteins comprising the desired protein linked to heterologous signal peptides is well known and widely practiced in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

8. With regard to the obviousness rejection of now canceled claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146, applicant argues that (1) Garger et al. teach the secretion of the recombinant human glucocerebrosidase by tobacco leaf cells to the interstitial fluid of tobacco plants and the deletion of vacuolar targeting sequences, thus teaching away from vacuolar targeting of the recombinant human glucocerebrosidase, (2) Boller et al. teach methods for expressing plant proteins naturally occurring in the vacuole which lack their vacuolar targeting signal peptides, citing sections of the reference of Boller et al. that teach secretion into the intercellular space by deleting the vacuolar targeting signal, and (3) Frijters et al. merely reports the sequence of an ER targeting signal having SEQ ID NO: 1. Applicant also submits that the claims have been amended to include the limitation of the glucocerebrosidase being linked at the C-terminus to the peptide of SEQ ID NO: 2, thus distinguishing the fusion protein of Garger et al., Boller et al. and Frijters et al. from the claimed invention.

9. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. It is noted that the amendments made to the claims do not distinguish the fusion protein of Garger et al., Boller et al. and Frijters et al. from the claimed invention because the fusion protein of Garger et al., Boller et al. and Frijters et al. has the human glucocerebrosidase of SEQ ID NO: 8 linked at its C-terminus to the peptide of SEQ ID NO: 2. Thus, it is unclear to the Examiner how the amendments made to the claims distinguish the claimed invention from that of the cited prior art.

With regard to the teachings of Boller et al., while it is agreed that Boller et al. teach deleting or inactivating the C-terminus vacuolar signal peptide to allow a protein which is naturally retained in the

vacuole to be secreted to the medium, Boller et al. also teach that (1) one of the advantages in directing proteins to the vacuole is the fact that vacuoles constitute the largest storage compartment in plants for dissolved substances (column 2, line 57-column 3, line 1), and (2) one could add the DNA encoding the vacuolar signal peptide to the 3' end of any desirable expressible DNA (C-terminus of the corresponding protein). Thus, simply because Boller et al. also teach situations when deleting the vacuolar signal peptide may be advantageous, is not sufficient for one of skill in the art to reasonably conclude that Boller et al. teach away from using a vacuolar signal peptide, particularly in view of the fact that Boller et al. teach advantages in directing proteins to the vacuole. With regard to the teachings of Frijters et al., it is noted that the ER targeting signal of SEQ ID NO: 1 is a functional equivalent of the ER targeting signal used by Garger et al. With regard to the teachings of Garger et al., it is noted that while it is agreed that Garger et al. teach that the protein was secreted via a default pathway into the apoplastic compartment, intercellular fluid, cell wall matrix materials, nothing in the teachings of Garger et al., or the prior art, indicates that directing the human glucocerebrosidase to the vacuole would have a negative effect on the protein. It is noted that a human protein would not have a vacuole targeting signal (vacuoles are only present in plants). Therefore, Garger et al. cannot teach deletion of a vacuole targeting signal in the human glucocerebrosidase of SEQ ID NO: 8. While it is agreed that Garger et al. teach the deletion of a few amino acids of the human glucocerebrosidase at the C-terminus which resulted in increased activity when the protein was secreted to the plant leaf, this is not tantamount to teaching that adding a vacuole targeting signal peptide to the C-terminus of a human protein so that the protein can be directed to the vacuole is detrimental to the human protein, or that it would affect its enzymatic activity. The teachings cited by applicant as being contrary to the idea of adding a vacuole targeting signal peptide to the human glucocerebrosidase of SEQ ID NO: 8 do not support applicant's position simply because (1) there are no vacuole targeting signal peptides in a human protein to delete, (2) Garger et al. were interested in secreting the human protein to the intercellular fluid, and (3) Garger et al. do not teach directing the

human glucocerebrosidase of SEQ ID NO: 8 to vacuoles, therefore they do not teach a vacuole targeting signal peptide. Simply because Garger et al. do not teach redirecting the protein of interest to the vacuole is not sufficient for one of skill in the art to reasonably conclude that Garger et al. teach away from redirecting the protein of interest to the vacuole. Thus, contrary to Applicant's assertions, neither the teachings of Garger et al., Boller et al. or Frijters et al. teach away from directing the human glucocerebrosidase to the vacuole. With regard to the argument that the protein of Garger et al. does not have exposed mannose glycan structure, it is noted that the fusion protein of Garger et al., Boller et al. and Frijters et al. would inherently have this structure as taught by the specification. Therefore, for the reasons of record and those set forth above, one of skill in the art would have to conclude that the claimed invention is obvious over the prior art of record.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 154-167 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-25 of copending Application No. 11/790991. This is a new rejection necessitated by amendment.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claims 154-167 are directed in part to (1) a protein which comprises SEQ ID NO: 14, (2) a plant cell comprising (1), and (3) a pharmaceutical composition comprising the plant cell of (2) or the protein of (1). Claims 23-25 of copending application No. 11/790991 are directed to a plant cell comprising a protein having the amino acid sequence of SEQ ID NO: 15. SEQ ID NO: 15 of copending application No. 11/790991 (506 amino acids) is comprised by SEQ ID NO: 14 of the instant application (amino acids 22-526 of SEQ ID NO: 14). The specification of copending application No. 11/790991 teaches the polypeptide of SEQ ID NO: 14 as a preferred embodiment of the genus of proteins comprising SEQ ID NO: 15. The specification also discloses the plant-glycosylated protein of SEQ ID NO: 14 as a preferred embodiment of the genus of plant-glycosylated proteins comprising SEQ ID NO: 15, wherein said protein comprises exposed mannose residues, a xylose residue and a fucose residue. Therefore, in view of the preferred embodiments disclosed in the specification of copending Application No. 11/790991, and the fact that a preparation comprising the cells of claims 23-25 is a preparation that comprises a protein comprising SEQ ID NO: 15, the invention of claims 154-167 is deemed an obvious variation of the invention of claims 23-25 of copending Application No. 11/790991.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. With regard to this rejection as it was previously applied to now cancelled claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146, applicant states that the cancellation of this rejection renders the previous rejection moot. Applicant also submits that issues of provisional obviousness-type double patenting and submission of terminal disclaimers will be further considered upon an indication of allowable subject matter. The examiner acknowledges applicant's remarks. However, as indicated above, a new rejection necessitated by applicant's submission of new claims has been issued, as explained above.

Conclusion

13. No claim is in condition for allowance.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

16. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (571) 272-0956. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
October 28, 2010